DETAILED ACTION

This application is a 371 of PCT/DK05/00068.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 5, 2010 has been entered.

Claims 1, 8-9, 11-16, 18, 43-49, and 51-69 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-2, 7-9, 11-16, and 18) in the reply filed on December 17, 2008 is acknowledged.

Newly submitted claim 67 is directed to an invention that lacks unity of invention from the invention originally claimed for the following reasons: claim 67 is drawn to a method of preparing a pharmaceutically acceptable formulation comprising a polypeptide with ASA activity. As discussed in the Requirement for Restriction, the technical feature linking Groups I-III and claim 67 is that they all relate to a human arylsulfatase. However, human arylsulfatase was known in the art and therefore the technical feature linking groups I-III and claim 67 does not constitute a special technical

feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 67 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on March 22, 2011 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

Applicant's amendment and arguments filed on September 10, 2009, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied.

Claim Objections

In view of the amendment, the objection to claim 11 has been **withdrawn.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 and claims 12-16, 18, and 68-69 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: step I. Claim 11 recites steps II-VI but does not recite step I.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

In view of the amendment, the rejection of claims 1, 8-9, 11-16, and 42-49 under 35 U.S.C. 102(b) as being anticipated by Fogh et al. has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8-9, 43-49, and 51-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fogh et al., Current Protocols in Protein Sciences, Wang et al., and Protein Purification Handbook.

Claims 1, 8-9, 43-49, and 51-67 are drawn to a method for production of a purified recombinant mature polypeptide with arylsulfatase A (ASA) activity in a continuous mammalian or human cell culture system by:

i. continuously culturing a mammalian or human cell capable of secreting said mature polypeptide into a liquid culture medium and

ii. purifying the mature polypeptide by

a) using an Expanded Bed Chromatography

b) passive step wherein the mature polypeptide with ASA activity passes through a cation exchange chromatography resin without binding thereto and

c) active step wherein the mature polypeptide with ASA activity is detained within and subsequently eluted from an anion exchanged membrane or

resin,

wherein the cation and anion exchange chromatography are coupled or connected in a series, said mammalian or human cell comprises a polynucleotide encoding a polypeptide of SEQ ID NO:2 or 3 and the mature polypeptide is post-transnationally modified product thereof and has a specific ASA activity of at least 20 units/mg and wherein the continuous culturing is for a period of at least one to four weeks and is carried out in a bioreactor which has a cell retention device is at least 95% efficient, medium comprising the polypeptide is collected at least daily while retaining cells in said bioreactor.

Fogh et al. (WO 02/098455 A2 – form PTO-1449) discloses a method for production of recombinant a recombinant human arylsulfatase A (rhASA) having 100% sequence identity to SEQ ID NO:2 or 3 of the instant invention by culturing a human cell producing rhASA in a batch system for about 163 hours comprising a bio-reactor by concentrating the rhASA by tangential flow filtration, using a DEAE sepharose column, using hydrophobic interaction column, using a polishing step comprising cation and anion exchange columns, using a viral reduction filter, formulating the rhASA in a buffer which comprises using a detergent (tween 80), and filling the rhASA into a container and freeze-drying the enzyme (pages 14-16 and 40-44 and Sequence Listing pages 1-3). The purified ASA of Fogh et al. has a specific ASA activity of at least 20 units/mg (page 28). Human ASA is an important enzyme useful for preventing or treating the developmental symptoms related to Metachromatic leukodystrophy (MLD) (page 1).

The difference between the above reference and the instant invention is that the reference does not teach a method of continuously culturing the mammalian or human cell for 1-4 weeks and carried out in a bioreactor which has a cell retention device is at least 95% efficient, medium comprising the polypeptide is collected at least daily while retaining cells in said bioreactor and nor explicitly teach a passive step wherein the polypeptide passes through a cation exchange resin/membrane without binding thereto.

However, Fogh et al. teaches that for the cation exchange step, the pH should be acidic (page 42). At acidic pH, the ASA polypeptide does not bind to the cation exchange resin/membrane.

The use of continuous culture systems is well known for producing large quantities of protein (Current Protocols in Protein Sciences (1998), pages 5.10.19 – form PTO-892). Continuous culturing for a period of 1-4 weeks, cell retention of at least 95% efficient, and collection of the medium at least daily while retaining cells in said bioreactor is well within the knowledge of one skilled in the art (see Current Protocols in Protein Sciences (1998), pages 5.10.19 and Wang et al. Biotechnol Bioeng. 2002 Jan 20;77(2):194-203 – form PTO-892). Using Exanded Bed Chromatography for capturing the polypeptide from a large sample is also well known (pages 16 and 93 of Protein Purification Handbook (2001) - form PTO-892).

Therefore, combining the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the method of Fogh et al. by using a continuous culture system to produce purified human ASA of Fogh et al. on a large scale.

One of ordinary skill in the art would have been motivated to combine the above references in order produce human ASA in large quantities, since human ASA is an important enzyme useful for preventing or treating the developmental symptoms related to Metachromatic leukodystrophy. One of ordinary skill in the art would have been motivated to use a continuous culture system in order to produce large quantities of human ASA.

One of ordinary skill in the art would have had a reasonable expectation of success since Fogh et al. teaches expression of human ASA in human and mammalian cells and outlines isolation and purification steps, use of continuous culture systems is routine in the art and strategy for purifying a protein comprising the steps of 1. prepration, extraction and clarification, 2. capture, 3. intermediate purification, and 4. polishing is known and disclosed by Fogh et al. and Protein Purification Handbook.

Therefore, the above references render claims 1, 8-9, 43-49, and 51-67 *prima facie* obvious.

Claims 1, 11-16, 18 and 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fogh et al., Current Protocols in Protein Sciences, Wang et al., and Sofer et al.

Claims 1, 11-16, 18 and 68-69 are drawn to a method for production of recombinant a recombinant human arylsulfatase A (rhASA) by

i. continuously culturing a mammalian cell producing a mature polypeptide with ASA activity in a continuous culture system and ii. purifying said polypeptide by:

I. concentrating the human ASA by tangential flow filtration,

II. using a DEAE sepharose column (anion exchange column),

III. using hydrophobic interaction column,

IV. buffer exchange using tangential flow filtration,

V. using a polishing step comprising cation and anion exchange columns,

a) passive step wherein the mature polypeptide with ASA activity passes through a cation exchange chromatography resin without binding thereto and

b) active step wherein the mature polypeptide with ASA activity is detained within and subsequently eluted from an anion exchanged membrane or resin,

wherein the cation and anion exchange chromatography are coupled or connected in a series and said mammalian or human cell comprises a polynucleotide encoding a polypeptide of SEQ ID NO:2 or 3.

VI. using a viral reduction filter,

VII. formulating the rhASA in a buffer which comprises using a detergent, and

VIII. filling the rhASA into a container and freeze-drying the enzyme.

Fogh et al. (WO 02/098455 A2 – form PTO-1449) discloses a method for production of recombinant a recombinant human arylsulfatase A (rhASA) having 100% sequence identity to SEQ ID NO:2 or 3 of the instant invention by culturing a human or

mammalian cell producing rhASA in a system for about 163 hours comprising a bio-reactor by concentrating the rhASA by

I. Concentration/diafiltration step: tangential flow filtration

II. Capture step: DEAE sepharose column (anion exchange column),

III. Intermediate step 1: hydrophobic interaction column,

IV: Intermediate step 2: several options are described,

V: polishing step: cation and anion exchange columns,

VI: Virus filtration step: a viral reduction filter,

VII: Diafiltration/Formulation step: formulating the rhASA in a buffer which comprises using a detergent (tween 80), and

VIII: Formulation, Filling and Freeze-drying: filling the rhASA into a container and freeze-drying the enzyme (pages 14-16 and 40-44 and Sequence Listing pages 1-3).

Fogh et al. also teaches that human ASA is an important enzyme useful for preventing or treating the developmental symptoms related to Metachromatic leukodystrophy (MLD) (page 1).

The difference between the above reference and the instant invention is that the reference does not teach a method of continuously culturing the mammalian or human cell for at least 1 week, explicitly teach a passive step wherein the polypeptide passes through a cation exchange resin/membrane without binding thereto and step IV: Intermediate step 2 using tangential flow filtration.

However, Fogh et al. teaches that for the cation exchange step, the pH should be acidic (page 42). At acidic pH, the ASA polypeptide does not bind to the cation exchange resin/membrane.

The use of continuous culture systems is well known for producing large quantities of protein (Current Protocols in Protein Sciences (1998), pages 5.10.19 – form PTO-892). Continuous culturing for a period of at least 1 week, cell retention of at least 95% efficient, and collection of the medium at least daily while retaining cells in said bioreactor is well within the knowledge of one skilled in the art (see Current Protocols in Protein Sciences (1998), pages 5.10.19 and Wang et al. Biotechnol Bioeng. 2002 Jan 20;77(2):194-203 – form PTO-892).

Tangential flow filtration is commonly used between the first intermediate step (hydrophobic interaction chromatography) and the polishing to reduce the volumn (see Figure 1 on page 25 of Sofer - form PTO-892). Diafiltration using tangential flow filtration is commonly used to exchange buffers and reducing the concentration of undesirable species (see pages 2-3 of Millipore - form PTO-892).

Therefore, combining the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the method of Fogh et al. by using a continuous culture system to produce, isolate and purify human ASA of Fogh et al. on a large scale and substitute or add a tangential flow filtration step in the Intermediate step 2 of Fogh et al.

One of ordinary skill in the art would have been motivated to combine the above references in order produce human ASA in large quantities, since human ASA is an

important enzyme useful for preventing or treating the developmental symptoms related to Metachromatic leukodystrophy. One of ordinary skill in the art would have been motivated to use a continuous culture system in order to produce large quantities of human ASA. One of ordinay skill in the art would have been motivated to substitute or add a tangential flow filtration step in Intermediate step 2 of Fogh et al. to enhance the purity or yield of the human ASA.

One of ordinary skill in the art would have had a reasonable expectation of success since Fogh et al. teaches expression of human ASA in human and mammalian cells and outlines isolation and purification steps, use of continuous culture systems is routine in the art, strategy for purifying a protein comprising the steps of 1. prepration, extraction and clarification, 2. capture, 3-4. intermediate purification, 5. Polishing, 6. Virus filtration, 7. Diafiltration/formulation, and 8. Formulation, filling and freeze-drying is known and disclosed by Fogh et al., steps 1-5 are also disclosed in Protein Purification Handbook, and use of tangential flow as step 4 was common knowledge and disclosed in Sofer.

Therefore, the above references render claims 1, 11-16, 18 and 68-69 *prima facie* obvious.

Conclusion

Claims 1, 8-9, 11-16, 18, 43-49, and 51-69 are pending.

Claim 67 is withdrawn.

Claims 1, 8-9, 11-16, 18, 43-49, 51-66 and 68-69 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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/Yong D Pak/
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